IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hans Rudolf MUELLER et al. Examiner: T. McKenzie

Serial No.: 09/551,405 Group Art Unit: 1624

Filed: April 17, 2000

For: STABLE CRYSTALLINE SALTS OF 5-METHYLTETRAHYDROFOLIC ACID

BRIEF ON APPEAL

I hereby certify that this correspondence is being deposited with the U.S. Postal Services as First Class Mail in an envelope addressed to Assistant Commissioner for Patents Washington, D.C. 20231 On: November 7, 2001
Name: Richard J. Traverso
SIGNATURE
DATE November 7, 2001

Honorable Commissioner of Patents
Washington, D.C. 20231

Sir:

Further to the Notice of Appeal filed on September 7, 2001, herewith are three copies of Appellants' Brief on Appeal. A check for the fee of $320.00 is enclosed. The Commissioner is hereby authorized to charge any additional fees for the papers being filed herewith, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

This is an appeal from the decision of the Examiner finally rejecting claims 1-3, 5-8, 10-13, 16 and 17 of the above-identified application.

(1) REAL PARTY IN INTEREST

The real party in interest in the present application is EPROVA AG, to whom the present application was assigned on June 5, 2000 and recorded on Reel 011055/Frame 0009.

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(2) RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences known to appellant or appellant's legal representative which will directly affect or be directly affected by or have any bearing on the Board's decision in the pending appeal.

(3) STATUS OF THE CLAIMS

Claims 1-8, 10-13 and 16-20 are pending in the present application. Claim 4 directed to a crystalline calcium salt of 5-methyl-(6S)-tetrahydrofolic acid and Claims 18-20 drawn to methods of producing 5-methyl-(6s)-tetrahydrofolic acid are allowed.

Claims 1-3, 5-8, 10-13, 16 and 17 are rejected and are the subject of this appeal. A copy of the rejected claims is provided in the Appendix.

(4) STATUS OF AMENDMENTS AFTER FINAL

An amendment to Claim 8 was proposed after final in a paper filed on September 7, 2001. The Examiner stated in the Advisory Action dated September 25, 2001, that the proposed Amendment would not entered with the filing of this of Appeal.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to Stable Crystalline Salts of 5-Methyltetrahydrofolic Acid, to the use thereof, and to a method of producing them, (see page 1, lines 3-6). Claims 1-7 are directed to crystalline salts of 5-methyltetrahydrofolic acids and claims 8-13 and 16-20 are directed to the methods for their production. The crystalline salts have an orderly molecular structure as illustrated by the X-ray diffraction spectra in Figs. 1-4. A comparison of Figures 1-4 to Figure 5 of the application shows the differences in the diffraction spectra (X-Ray Powder Plots) of crystalline samples (Figures 1-4) and amorphous samples of 5-methyltetrahydrofolic acid (Figure 5). The crystalline forms of these salts have been found to exhibit excellent stability, (see page 2, lines 5 and 17-18 of the specification) when compared with amorphous specimens (see Example 1).

As stated on page 3 of the specification, crystallization is preferably effected from solutions of the salt of 5-methyltetrahydrofolic acids but can also be effected from a suspension.

As discussed in the disclosure at page 3, lines 3-5 and illustrated in the Examples of the application, the crystalline form of the calcium salts of 5-methyltetrahydrofolic acid are recovered from a polar medium (water) following a thermal treatment (heating). Example 4 of this application shows that the amorphous structure is obtained when the calcium salt is isolated from a polar medium without a thermal treatment. Different crystalline forms are obtained by different treatments as discussed more particularly on page 3, lines 24-32 and illustrated in Figs. 1-4.

(6) ISSUES

(1) Whether claims 1-3, 6-7 and 10-13 are anticipated by Scheib (U.S. Patent No. 5,457,202) under 35 U.S.C. § 102(b).

(2) Whether claims 1-3 and 5-7 are anticipated by Muller (U.S. Patent No. 5,006,655) under 35 U.S.C. § 102(b).

(3) Whether claims 1 and 2 are anticipated by Marazza (U.S. Patent No. 5,194,611) under 35 U.S.C. § 102(b).

(4) Whether claims 1-3, 6-7, 10, 11, 13, 16 and 17 are anticipated by Vecchi (U.S. Patent No. 5,350,850) under 35 U.S.C. § 102(b).

(5) Whether claims 1, 3, 6 and 7 are anticipated by Gennari (U.S. Patent No. 5,223,500) under 35 U.S.C. § 102(b).

(6) Whether claim 8 satisfies the requirements of 35 U.S.C. § 112, second paragraph.

(7) Whether claim 12 satisfies the requirements of 35 U.S.C. § 112, first paragraph.

(7) GROUPING OF THE CLAIMS

Issue 1: Method Claims 10-13 do not stand or fall together with composition claims 1-3 and 6-7 with respect to this issue.

Issue 4: Claims 1-3 and 6-7, composition claims, do not stand or fall together with claims 10, 11, 13, 16 and 17, method claims, with respect to this issue.

Issue 6: Claim 8 is the only claim rejected and stands separate from the rest of the claims with respect to this issue.

Issue 7: Claim 12 is the only claim rejected and stands separate from the rest of the claims with respect to this issue.

(8) APPELLANTS' ARGUMENTS

1) **Whether Claims 1-3, 6-7 and 10-13 are anticipated by Scheib U.S. Patent 5,457,202 under 35 USC §102(b)**

Scheib U.S. 5,457,202, is directed to a method of resolving 5-methyltetrahydrofolic acid from a racemic mixture of the (6R, 6S) form and does not disclose that any of the isolated salts have an orderly molecular structure consistent with crystallinity. The solids recovered in Example 2 of Scheib are identified as "crystals" but there is no indication these solids have an orderly molecular structure consistent with crystallinity. Without such information or an analysis by X-ray diffraction, one skilled in the art would assume that the use of the term "crystals" simply refers to the solids visual appearance. The reference to 5-methyltetrahydrofolic "crystals" is not a literal disclosure of the compositions claimed herein.

There is also no evidence that the solids recovered by Scheib inherently have an orderly molecular structure consistent with crystallinity. The methods used to recover the solid salts are distinct from those disclosed in the present invention which are shown to provide "crystalline" solids. At column 1, lines 47-52, Scheib describes heating and cooling a racemic mixture of pyrrolidine salts of folic acid and not calcium salts of folic acid as described in the examples of the present application or salts of other alkaline earth metals. In Examples 1-4 of Scheib, pyrrolidine salts are recovered from solution and not calcium salts.

The preparation of calcium salts in water is described at col. 1, lines 53-56, of Scheib but these methods do not involve heating the calcium salt in a polar medium and the recovery of these salts from this polar medium water after heating. The procedure given for recovering calcium salts is consistent with Example 4 of the present application, which is shown to provide salts with an amorphous structure.

In that this reference does not disclose that the 5-methyltetrahydrofolic acid salts recovered have an orderly molecular structure consistent with crystallinity and the 5-methyltetrahydrofolic acid salts recovered do not inherently have a such an orderly molecular structure consistent with the compounds claimed herein, composition claims 1-3 and 6-7 are not anticipated by this reference.

The crystalline calcium salts defined and claimed in claims 3, 6 and 7 are clearly not

anticipated in that the methods described by Scheib for isolating such salts are consistent with the procedures shown in Example 4 of this application, which produce an amorphous structure.

As for method claims 10-13, there is no evidence the procedure performed by Scheib would provide crystalline salts of 5-methyltetrahydrofolic acid. Scheib never indicates that the products obtained have an orderly molecular structure consistent with crystallinity and the methods described are not shown to inherently provide for such crystallinity. As discussed above, Scheib employs only heat treatments with pyrrolidine salts. These pyrrolidine salts are distinct from the calcium salts which Applicants have prepared and therefore, Applicants disclosure provides no evidence that the pyrrolidine salts obtained by Scheib are inherently crystalline. Where Scheib isolates calcium salts of 5-methyltetrahydrofolic acid, the heat treatment is not used and therefore, such a method does not inherently provide a crystalline salt as shown by Example 4 of the present application. Since the methods of Scheib are not shown to provide crystalline salts of 5-methyltetrahydrofolic acid and they do not inherently provide such crystalline salts, method claims 10-13 are not anticipated by this reference.

2) **Whether claims 1-3 and 5-7 are anticipated by Müller (U.S. Patent No. 5,006,655) under 35 USC §102(b)**

Müller '655 provide no hint or suggestion that the tetrahydrofolic acid salts recovered have an orderly molecular structure consistent with crystallinity. No X-ray diffraction data is provided as evidence of such a structure. Reference is made to "fractional crystallization" but there is no evidence or indication that this technique provides products with an orderly molecule structure. In the absence of this information, one skilled in the art would assume that the term "crystallization" refers to the visual appearance of the solids. Therefore, the reference to products obtained by fractional crystallization is not a literal disclosure of the compositions claimed herein.

There is also no evidence that the salts recovered by Müller inherently have an orderly molecular structure consistent with crystallinity. The methods described are primarily directed to isolating the enantiomers in a solvent other than water (formic acid). The recovered enantiomers are then converted to calcium salts but these salts are recovered from solution without a heat treatment step, which is inconsistent with the methods of the present

invention. Muller '655 add calcium chloride to a solution of the tetrahydrofolic acid to form the calcium salts after the solution is cooled. (See Example 1). Therefore, the solutions of the calcium salt are not thermally treated. In Example 2, the calcium salt is also formed and recovered without heating. The techniques described by Müller '655 are consistent with those of Example 4 of the present application which provide solid 5-methyltetrahydofolic acid with an amorphous structure. Therefore, in the absence of any evidence that the salts of Müller '655 have an orderly molecular structure consistent with crystallinity, the subject matter of claims 1-3 and 5-7 is not anticipated by this reference.

3) **Whether claims 1 and 2 are anticipated by Marazza (U.S. Patent No. 5,194,611) under 35 U.S.C. § 102(b)**

Marazza '611 describe the separation of racemic mixtures by "fractional crystallization." However, Marazza does not disclose that an orderly molecular structure is present in the salts of the tetrahydrofolic acid that are recovered. No X-ray diffraction spectra were taken such that one skilled in the art would assume that the term "crystallization" is intended to mean the solids take a definite form or shape that is recognized visually. One skilled in the art would not assume that these solids have an orderly arrangement of molecules without such data or an express indication that such an orderly structure is present. As shown in Example 4 of this application, solid 5-methyltetrahydrofolic acid salt recovered from a solution can be amorphous and the formation of solids from solution does not necessarily provide an orderly molecular structure consistent with crystallinity.

There is also no evidence to suggest that the solids recovered by Marazza '611 are inherently orderly in structure (crystalline). In the method disclosed at col. 4 of Marazza '611, an ammonium salt of tetrahydrofolic acid is heated to 50 to 60°C. This ammonium salt form is distinct from the calcium salts (and other alkaline earth metal salts) used in the present invention to prepare a crystalline form. Therefore, Applicants disclosure provides no evidence that the heat treatment of the ammonium salt of Marazza '611 would inherently provide a crystalline form.

The preparation and recovery of the calcium salt of 5-methyltetrahyofolic acid is described at col. 5, lines 1-12 of Marazza '611. There is no indication that this solution is heated before the separation and recovery of the solid salt. In addition, it is indicated that the

salts are "precipitated". These techniques are clearly inconsistent with the procedures described in the present application for the preparation of salts with an orderly molecular structure.

Due to the distinct methods disclosed by Marazza '611, particularly with respect to heating of the calcium salt solutions, and the absence of any evidence that the salts recovered by Marazza '611 have an orderly molecular structure, this reference does not anticipate the compositions of claims 1 and 2.

Example 2 of Marazza '611 discloses the isolation of 6R, N-methyltetrahydrofolic cyclohexyl ammonium salt. This product is referred as "crystalline solid" but there is no evidence the cyclohexyl ammonium salts of the tetrahydrofolic have an orderly molecular structure consistent with crystallinity. One skilled in the art would assume the "crystalline solids" refers to the visible appearance of the solid and not its molecular structure, particularly since no X-ray diffraction data is provided.

Examples 3 and 4 of Marazza '611 describe the preparation of tetrahydrofolic acid calcium salts. This is accomplished without a heat treatment step, which suggests an amorphous structure is obtained, consistent with solids obtained in Example 4 of this application.

4) **Whether claims 1-3, 6-7, 10, 11, 13, 16 and 17 are anticipated by Vecchi (U. S. Patent No. 5,350,850).**

It is alleged that claims 1-3, 6-7, 10, 11, 13, 16 and 17 are anticipated by Vecchi '850. The product of Vecchi is clearly different than the product claimed in the current application. Vecchi describes his product as needing to be filtered and dried in a drier under vacuum avoiding light and contact with oxygen. See Vecchi column 3, lines 50-51. In contrast, the products of the current invention are stable at room temperature, practically without limitations. See specification page 2, lines 7-9. Therefore, the two products, one being sensitive to oxygen and light and the other not, are clearly not the same, hence the earlier can not anticipate the later, the current invention.

The methods of this invention do not require vacuum to avoid oxygen in isolating the product and so the claimed methods are also not anticipated.

5) **Whether claims 1, 3, 6 and 7 are anticipated by Gennari (U.S. Patent No. 5,223,500).**

The products of Geranni are clearly different than the products of the current invention. On column 4, lines 39-40, Geranni discloses that self-oxidation problems occur in preserving the 5-methyltetrahydrofolic acid. The specification of the current application indicates the inventive salts exhibit a stability of 99.1% after 12 months when stored in air at 25°C and at a 60% relative humidity. Even after 88 months of storage, the inventive salts show a stability of 97.8%. The product of Geranni is not the same as the product of the current invention as it is admitted to have a self-oxidation problem while the salts of the current invention do not.

Geranni also discloses that the entire production process is conducted in the presence of inert gas, and in some steps in the presence of a reducing agent to prevent self-oxidation. See column 4, lines 32-35. The processes disclosed in Examples 5-9 of the current application's specification were conducted without any inert gas or any other purge to preclude oxygen. It is therefore requested that the anticipation rejection based on this reference be reversed as it is clear that the products disclosed by Geranni are not the same as those claimed herein.

6) **Whether claim 8 satisfies the requirements of 35 U.S.C. § 112, second paragraph.**

Claim 8 is rejected under 35 USC §112, second paragraph for its recitation of the phrase "from the resulted heated solution." It is alleged this phrase is indefinite. A person of ordinary skill in the art reading the claim would understand that the resultant heated solution refers to the 5-methyl-(R,S)-,-(6S)- or (6R)-tetrahydrofolic acid in a polar medium subjected to a thermal treatment at a temperature above 60°C recited earlier in the same claim. Claim 8 is therefore not indefinite and reversal of this rejection is therefore respectfully requested.

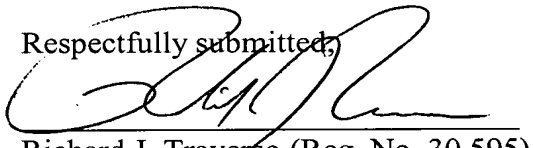
7. **Whether claim 12 satisfies the requirements of 35 U.S.C. § 112, first paragraph.**

Claim 12 is rejected under 35 USC §112, first paragraph for the recitations "crystallization is effective from the suspension," recited therein. It is alleged that the

compound must be dissolved in order for it to be recrystallized. Claim 12 is intended to define embodiments wherein the crystalline salts are dissolved within the medium that also contains undissolved materials, hence it would be more precise to refer to them as a suspension. In referring to a "crystallization from a suspension" applicants intend to define a crystallization wherein at no point a clear solution exists. Using different terminology would not convey the meaning that applicants intend. Claim 12 is adequately enabled as one skilled in the art would immediately understand the difference between a solution and a suspension. Reversal of this rejection is therefore respectfully requested.

Based on the above remarks, reversal of all of the Examiner's rejections is earnestly solicited.

Respectfully submitted,



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APPENDIX

1. A crystalline salt of 5-methyl-(6R,S)-, -(6S)- or -(6R)-tetrahydrofolic acid, said crystalline salt having a water of crystallization of at least one equivalent per equivalent of 5-mthyltetrahydrofolic acid.

2. A crystalline salt according to claim 1, of 5-methyl-(6S)- or -(6R)-tetrahydrofolic acid.

3. A crystalline calcium salt according to claim 1, of 5-methyl-(6S)- and -(6R)-tetrahydrofolic acid having ≥ 3 equivalents of water.

5. A crystalline calcium salt according to claim 1, of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 5.3, 6.9, 18.7 and 21.1 (Type II).

6. A crystalline calcium salt according to claim 1, of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.8, 10.2, 15.4 and 22.5 (Type III).

7. A crystalline calcium salt according to claim 1, of 5-methyl-(6S)-tetrahydrofolic acid with 2 theta values of 6.6, 15.9, 20.2 and 22.5 (Type IV).

8. A method of producing crystalline salts of 5-methy-(6R,S)-, -(6S)- and 5-methyl-(6R)-tetrahydrofolic acid, comprising subjecting a salt of 5-methyl-(6R,S)-, -(6S)- or –(6R)-tetrahydrofolic acid in a polar medium to a thermal treatment at a temperature above 60° Celsius and thereafter crystallizing said salt within said polar medium at room temperature or above.

10. A method according to claim 8, wherein the crystallisation is effected after thermal treatment at a temperature above 85 °C.

11. A method according to claim 8, wherein the crystallisation is effected from a solution.

12. A method according to claim 8, wherein the crystallisation is effected from a suspension.

13. A method according to claim 11, wherein the crystallisation is effected from water or from a mixture of water and an organic solvent which is miscible with water.

16. A method according to claim 8, wherein said salt is an alkaline earth salt.

17. A method according to claim 8, wherein said salt is calcium.

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